108 Comparative *in vitro* characterisation of colistimethate sodium 1 MIU/3 ml versus 2 MIU/4 ml in an eFlow® rapid Nebuliser

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The advantages of nebulised colistimethate sodium (CMS) in the treatment of cystic fibrosis (CF) have been shown in a number of clinical trials. Its widespread use over four decades has proven its safety and efficacy. The treatment of lung infections by inhalation of CMS offers the possibility to achieve high antibiotic drug concentrations at the airway surface. A product offering the advantage of two CMS dose strengths, 1 MIU ColiFin® in 3 ml 0.9% saline and 2 MIU ColiFin® in 4 ml 0.9% saline, was aerosol characterised in-vitro after nebulisation with an eFlow® rapid electronic nebuliser. The delivered dose was assessed by breath simulation experiments. NGI experiments were conducted to measure the size distribution of the aerosol. The respirable dose (RD) representing the amount of drug in droplets <5 μm was calculated.

In-vitro results for the eFlow® *rapid* loaded with 1 MIU of CMS dissolved in 3 ml saline indicated a delivered dose of 27.0 mg after 3.8 min of nebulisation. The observed MMAD was 4.1 μm and the calculated respirable dose was 18.0 mg CMS in droplets <5 μm. For 2 MIU of CMS dissolved in 4 ml saline a delivered dose of 57.8 mg was obtained with a nebulisation time of 6.2 min. The respirable dose was 40 mg (droplets <5 μm). Charging the eFlow® *rapid* with 2 MIU CMS/4 ml results in a twofold higher respirable dose taking only about 2.5 more minutes for inhalation compared to the lower dose strength (1 MIU/3 ml). Patients in need of high dose CMS inhalation may prefer ColiFin® 2 MIU nebulised with the eFlow® *rapid* due to its short nebulisation time coupled with a reliable twofold respirable dose.

109 In-vitro aerodynamic droplet characteristics of tobramycin (75 mg/ml) when nebulised by a Pari LC® Plus and an I-Neb

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We have adapted standard compendial methodology to characterise the aerodynamic droplet characteristics (ADC) of nebulisers by incorporating breath simulation (BS). Using this methodology we have determined the ADC of tobramycin 75 mg/ml (Bramitob, Chiesi, Italy) for 4 ml nebulised by a Pari LC® plus with a TurboBoy compressor (PARI, GmbH) and for an I-Neb, 300 μl cup (Philips Respironics, UK). The schematic design was BS (500 ml tidal volume, inhalation:exhalation ratio of 1:2), inhalation filter (IF), cooled Next Generation Impactor (NGI, operated at 15 L/min), nebuliser (NEB), supplementary air (15 L/min) and an exhalation filter (EF). The results are presented in the table.

Mean (SD) data (n = 10)

	PARI	I-NEB
NEB (mg)	202.8 (37.2)	5.5 (2.4)
TED ex NEB (mg)	119.1 (20.8)	15.5 (2.4)
IF (mg)	32.4 (12.1)	4.4 (1.4)
EF (mg)	10.3 (5.2)	0
Tubing (mg)	13.7 (8.7)	1.0 (0.6)
FPF (%)	64.9 (4.5)	53.3 (9.9)
MMAD (μg)	3.8 (0.3)	4.4 (0.2)
GSD	2.1 (0.2)	1.7 (0.1)

FPF: fine particle fraction; MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation.

From these data the fine particle dose (FPD) from I-Neb would be 8.3 mg. Separate determinations using PARI without the NGI and supplementary air proved an IF ex neb of 26.9(0.6) mg hence a FPD of 17.5 mg.

The results highlight the use of our adapted compendial methodology to enable ADC of breath enhanced nebulisers. Comparison of the FDPs suggests that 2 separate doses of Bramitob nebulised using an I-Neb with a 300 μl cup size could be comparable to 4 ml nebulised by a the PariLC+.

110 Head-to-head comparison of two inhaled tobramycin solutions in cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* (Pa) infection

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Objectives: Two aerosolized solutions of tobramycin are currently available in Europe: BRAMITOB® (300 mg/4 mL) and TOBI® (300 mg/5 mL). Their efficacy and safety were compared in CF patients with chronic Pa infection.

Methods: In a multinational, multicentre, open-label, non-inferiority trial, 324 CF patients aged ⩾6 years, with chronic Pa infection and forced expiratory volume in one second (FEV_1) ⩾ 40% and ⩽ 80% predicted were randomized to 28-day twice daily treatment with BRAMITOB or TOBI, followed by 28 days without treatment. The primary endpoint was FEV_1 % predicted change from baseline at day 28. Secondary endpoints included Pa density. Safety was assessed through adverse events (AEs) monitoring.

Results: After 28 days, there was an increase in FEV_1% predicted in both groups over baseline: 6.99% for BRAMITOB and 7.51% for TOBI. The least squares means were 4.66 for BRAMITOB and 5.16 for TOBI [difference: −0.50; two-sided 95% CI: (−2.58, 1.59); ANCOVA], with significant changes within each group ($p < 0.001$). After the 28-day "off" period, FEV_1 % predicted decreased, but an increase over baseline was maintained (5.47% for BRAMITOB and 5.37% for TOBI). There was a significant reduction of Pa density in sputum in both groups: −2.06 $\log_{10}$ CFU/g for BRAMITOB ($p < 0.001$) and −1.90 for TOBI ($p < 0.001$). Similar percentages of patients in both groups reported AEs. Cough was the most frequent drug-related AE for TOBI group (2.4%), compared to no patients in the BRAMITOB group.

Conclusion: BRAMITOB showed similar efficacy to TOBI, with significant improvement in pulmonary function and decreased Pa density in sputum. Both treatments were safe.

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111 Comparison of two inhaled tobramycin solutions in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection: results in different age subgroups

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Objectives: BRAMITOB® (300 mg/4 mL) and TOBI® (300 mg/5 mL) are the two tobramycin aerosolized solutions available in Europe. Their efficacy on lung function considering different age classes was compared in cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* (Pa) infection.

Methods: In a multinational, multicenter, open-label, controlled trial, a total of 324 CF patients aged ⩾6 yrs, with chronic Pa infection and forced expiratory volume in one second (FEV_1) ⩾40% and ⩽80% predicted were randomised to 28-day twice daily treatment with BRAMITOB or TOBI. We examined efficacy on lung function in different age classes: children 6–12 yrs, adolescents 13–17 yrs, adults ⩾18 yrs.

Results: Among 321 patients, 103 were children, 111 were adolescents and 107 were adults. Statistically significant improvements in FEV_1 % predicted, adjusted by age in classes, were observed at day 28, with no differences between the two tobramycin solutions. Greater benefits were observed in children and adolescents. Mean improvements for BRAMITOB: 9.2% in children (95% CI 6.0; 12.5), 7.3% in adolescents (95% CI 4.8; 9.8), 5.0% in adults (95% CI 2.8; 7.3); for TOBI: 9.2% in children (95% CI 6.6; 11.9), 9.6% in adolescents (95% CI 7.0; 12.1), 3.6% in adults (95% CI 1.2; 5.9). Similar findings were obtained for other pulmonary function measures, i.e. forced vital capacity (FVC) and forced expiratory flow at 25–75% FVC ($FEF_{25-75\%}$).

Conclusion: Tobramycin aerosolized solution improved lung function in all age groups, with greater benefits reported in children and adolescents. No differences were detected between BRAMITOB and TOBI.

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